



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: David A. Cheresch et al.)
Application No. 09/538,248)
Filed: March 29, 2000)
For: METHODS USEFUL FOR TREATING)
VASCULAR LEAKAGE AND EDEMA)
USING SRC OR YES TYROSINE)
KINASE INHIBITORS)
Examiner: Rebecca Prouty) Attorney Docket No. TSRI 651.3

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RESPONSE UNDER RULE 116

Box AF
Commissioner for Patents
Washington, D. C. 20231

Sir:

This communication is submitted in response to the Office Action dated 2 October 2002 on the above-identified application. Claims 1-4 and 16-20, inclusive, are under consideration.

The courtesies extended to Dr. Cheresch and the applicants' representatives during an interview held on 5 November 2002 are gratefully acknowledged. During the interview, the state-of-the-art pertaining to Src family tyrosine kinases and their activation was discussed, as well as distinctions of the present claims over the applied references. These distinctions are reiterated hereinbelow.

The claims presently under consideration are directed to amelioration of tissue damage related to vascular leakage by treating the involved tissue with a Src family tyrosine kinase inhibitor. It is the applicants' position that, in view of the state-of-the-art, one of ordinary skill would not have had a reasonable expectation of success that the inhibition of Src tyrosine kinase would reduce damage to tissue subject to vascular leakage or edema because Src tyrosine kinases are activated by many different growth factor dependent pathways. For example, VEGF and bFGF both promote angiogenesis and activate Src, Thomas et al., Ann. Rev. Cell Dev. Biol. 13:513-609 at 536 and 557 (1997), only VEGF

mediates vascular permeability. Thus, it would not have been obvious to one of ordinary skill that blocking of Src would somehow reduce VEGF-specific action such as vascular permeability or diseases associated therewith.

While there exists prior art that suggests that VEGF induces vascular permeability, there is also relatively recent prior art, such as Losordo et al., *Circulation* 98:2800-2804 (1998), and Hayashi et al., *J. Cereb. Blood Flow Metab.* 18(8): 887-895 (1998), that teach that the administration of VEGF to patients suffering from myocardial ischemia may be beneficial and reduces edema formation as well as neuronal cell damage. Hayashi et al. further note at page 894 that treatment with VEGF might become an effective means of therapy for ischemic stroke. Such teachings point one of ordinary skill away from the claimed invention.

The state-of-the-art review provided by Dr. Cheresh during the interview is reiterated in the Declaration by Dr. Cheresh filed concurrently herewith. Losordo et al. and Hayashi are Exhibits B and E, respectively, attached to the Cheresh Declaration.

The rejection of claims 1-4 and 16-20 under 35 U.S.C. 103(a) as unpatentable over any one of van Bruggen et al., Aiello et al. (U.S. Patent No. 6,284,751) or Jirousek et al. (U.S. Patent No. 6,093,743) in view of Munshi et al. is not warranted, and is hereby traversed.

The Aiello et al. and Jirousek et al. references are not only cumulative to one another, but also are not relevant. Both of these references are directed to a β -isozyme selective PKC inhibitor that counteracts the effects of VEGF but is not a VEGF inhibitor.

van Bruggen et al. on the other hand, describes the inhibition of VEGF with a fusion protein mFlet (1-3)-Ig G. van Bruggen et al. at page 1613 also note that

"The role of VEGF in the pathogenesis of stroke and in the formation of cerebral edema is unclear with contradictory experimental observations cited in the literature."

It is significant that van Bruggen et al. does not mention Src family tyrosine kinase, or its inhibition, for any purpose. van Bruggen et al. also contains no suggestion that activation of a Src family tyrosine kinase is responsible for vascular permeability. van Bruggen et al. describe VEGF antagonism, not Src tyrosine kinase inhibition. Thus, van Bruggen et al. clearly would not have led one of ordinary skill to conclude that Src kinase activation is an

early event in the VEGF signaling pathway as contended by the Examiner. As the Examiner has recognized, however, Src is well known in the art as being expressed in all cell types. There also are many pathways for activating Src family tyrosine kinases, see Declaration of David A. Cheresch, Ph.D., ¶¶ 18 & 19, that militate against the targeting of Src family tyrosine kinase for inactivation.

The foregoing defects of van Bruggen et al. are not cured by the Munshi et al. reference which does not even suggest reduction of vascular permeability. Thus, one of ordinary skill would not even turn to Munshi et al. when seeking to improve on VEGF inhibition as described by van Bruggen et al. Munshi et al. also state at page 1171 that PP1 did not inhibit VEGF stimulated Flk-1/KDR autophosphorylation. PP1 is not a VEGF inhibitor. Thus, one of ordinary skill would not seek to replace the fusion protein mFlt(1-3)-Ig G of van Bruggen et al., a VEGF antagonist, with PP1 when seeking to effect VEGF inhibition. Also, the extrapolation of the teachings of Munshi et al. beyond KS cells is clearly unwarranted. Munshi et al. merely speculate that Src kinase may act to link pathways from the VEGF receptor to mitogen-activated protein kinase and cytoskeletal components, thereby effecting tumor proliferation and migration.

To summarize, VEGF is not a Src family tyrosine kinase, but a multi-functional cytokine (Cheresch Declaration, ¶ 8), there is more than one VEGF signaling pathway (Cheresch Declaration, ¶ 7), and PP1 does not inhibit VEGF (Munshi et al.). Even the combination of van Bruggen et al with Munshi et al., assuming *arguendo* that such a combination is warranted, does not show or suggest that activation of Src family tyrosine kinases is responsible for vascular permeability. The prior art of record does not provide any suggestion to one of ordinary skill to focus on Src family tyrosine kinase inhibition when seeking to ameliorate tissue damage due to vascular permeability. Accordingly, there is no motivation that one of ordinary skill can glean from the applied references to inhibit Src family tyrosine kinase activity in order to ameliorate tissue damage due to vascular permeability. Withdrawal of the rejection is earnestly urged.

The further rejection of claims 1-4 and 16-20 under 35 U.S.C. 103(a) as unpatentable over any one of van Bruggen et al., Aiello et al. or Jirousek et al. in view of

Hanke et al. and either He et al. or Cooke et al. is likewise unwarranted, and is hereby traversed.

Aiello et al. and Jirousek et al. are cumulative to one another, and inapposite for reasons stated above.

van Bruggen et al. fails as a reference against these claims as discussed in detail hereinabove. Neither Hanke et al. nor the combination therewith of He et al. or Cooke et al. cure the aforementioned effects.

To reiterate, van Bruggen et al. describe inactivation of VEGF, not inactivation of Src family tyrosine kinase. Hanke et al. teach that inhibition of tyrosine kinases is an unpredictable art. van Bruggen et al., however, is not directed to inhibition of kinases but to inhibition of VEGF. Thus, one of ordinary skill would have had no motivation whatsoever to attempt to combine the teachings of Hanke et al. with those of van Bruggen et al. Any attempt to combine the teachings of these two references can only be based on an impermissible reliance on applicants' own disclosure.

While Hanke et al. shows that PP1 does inhibit Src family tyrosine kinase, Hanke et al. does not provide any motivation whatsoever to one of ordinary skill to do so in order to ameliorate tissue damage due to edema or vascular permeability. At most, the teachings of Hanke et al. are but an invitation to experiment that does not vitiate patentability.

The further consideration of the teachings of He et al. or Cooke et al. also does not support the attempted rejection of claims 1-4 and 16-20, inclusive.

As a matter of fact, He et al. support the applicants' position of unobviousness. He et al. unequivocally state at page 25130 that post-receptor signaling pathways of VEGF are not yet fully understood. See also Declaration of Cheresch, ¶ 12. Thus, the teachings of He et al. could not have provided any guidance, suggestion, or motivation to one of ordinary skill, to seek to inhibit a Src family tyrosine kinase in order to ameliorate tissue damage due to edema or vascular permeability. He et al. also does not provide any connection between PP2 inhibition and vascular permeability. Moreover, PP2 is not an antagonist of VEGF.

Likewise, Cooke et al. do not cure any of the foregoing defects of van Bruggen et al., Hanke et al. and He et al. as references, alone or in combination, against the present claims. Amelioration of tissue damage due to vascular permeability or edema by inhibition of

Src family tyrosine kinase is neither mentioned nor suggested. Cooke et al. also provide no basis for the conjecture that phosphorylation of VE-cadherin is the effector for the ... "increased vascular permeability signaled by VEGF," especially in view of the fact that even the role of VEGF in inducing vascular permeability is not fully understood. See also Declaration of Cheres, ¶¶ 7, 12 and 20.

The further rejection of claims 1-4 and 16-20 under 35 U.S.C. 103(a) as unpatentable over any one of van Bruggen et al., Aiello et al. or Jirousek et al. in view of Hanke et al. and Eliceri et al. (1998) is traversed as well.

As pointed out above, both Aiello et al. and Jirousek et al. are inapposite, inasmuch as these references do not pertain to VEGF inactivation or Src family tyrosine kinase inactivation in any way. Moreover, vis-a-vis one another, these references are cumulative.

van Bruggen et al. fail as a reference against claims 1-4 and 16-20, inclusive, for the detailed reasons discussed hereinabove. Hanke et al. likewise does not cure the deficiencies of van Bruggen et al. for reasons discussed hereinabove. Hanke et al. is nothing but an invitation to experiment. Furthermore, there is no motivation provided within the four corners of either van Bruggen et al. or Hanke et al. to warrant the attempted combination of these two references as references against the claims here under consideration. As pointed out hereinabove, PP1 is not a VEGF antagonist, thus one of ordinary skill would not have attempted to substitute PP1 for the VEGF antagonist mFt (1-3)-Ig G of van Bruggen et al.

Likewise, there is not valid basis for the attempted combination of Elicieri et al. with van Bruggen et al., or the combined teachings of van Bruggen et al. and Hanke et al. Elicieri et al. teach that Src family tyrosine kinase activity is needed for VEGF induced angiogenesis, thus one of ordinary skill would not have been inclined to inhibit such activity when seeking to promote tissue repair or ameliorate tissue damage. Angiogenesis clearly is important for cell proliferation, and for supplying oxygen to tissue. Query, why would one of ordinary skill have wanted to inhibit cell proliferation in injured tissue as well as limit oxygen supply? If anything, Eliceri et al. would have suggested to one of ordinary skill that VEGF activity should be enhanced rather than diminished when seeking to treat injured tissue,

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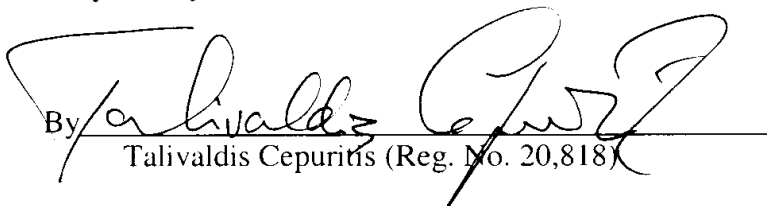
especially in view of Losordo et al. and Hayashi et al. (Exhibits B and E to Cheresch Declaration).

Form PTO/SB/08B listing the publications referred to herein and in Dr. Cheresch's Declaration is submitted herewith together with our check in the amount of \$180.00.

The foregoing discussion and the Declaration of David A. Cheresch, Ph.D. are deemed to dispose of all issues in this case and to place this application in condition for allowance. Early such action is solicited.

Respectfully submitted,

March 13, 2003

By 
Talivaldis Cepuritis (Reg. No. 20,818)

OLSON & HIERL, LTD.
20 North Wacker Drive
36th Floor
Chicago, Illinois 60606
(312) 580-1180